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Hodgkin's Disease

A Clinical-Pathological Review of 150 Cases

WARREN L. BOSTICK, M.D., *San Francisco*

SUMMARY

One hundred and fifty cases of Hodgkin's disease were analyzed in an effort to detect significant clinical-pathological correlations and to elucidate any possible factors of prognostic or etiological importance.

A relatively long survival for patients with Hodgkin's paragranuloma was not noted in this series. Instead the survival rate among them was closely parallel to that of patients with classical granuloma. Hodgkin's sarcoma is a more malignant disease with a patient survival rate not more than half that of patients with the granuloma variety. It is not necessarily a disease of older age groups. Great caution must be exercised to avoid including non-Hodgkin's disease tumors under the heading of Hodgkin's sarcoma or paragranuloma.

The series reported corresponds with many other reported series of Hodgkin's disease as regards greater incidence in males and longer survival in females. In this series the cases in patients under the age of 15 were all in males. The predominance of initial enlargement of the cervical nodes was again noted in this series, as was the high proportion of negative reaction to tuberculin tests. The incidence of tuberculous lesions in patients who died of Hodgkin's disease was only slightly greater than in those who died of other lymphoma. Site of origin of the disease apparently affects survival time. There was statistical evidence that gonadal activity might influence the equilibrium of the disease.

Lymph node bacteriological cultures were not remarkable. Brucella organisms were absent. Fertile egg passages for detecting possible viral agents revealed increased egg mortality and cutaneous sensitivity reactions to the harvested amniotic fluid.

IN THE last 25 years there have been studied at the University of California Hospital 150 cases of microscopically proven Hodgkin's disease. From this group, biopsy slides are available from 123, and 33 complete autopsy examinations have been done. This material is being critically reviewed with the object of comparing its characteristics with other reported series of Hodgkin's disease cases, of elucidating certain details of histologic-clinical correlation, and of searching for any factors of possible prognostic or etiologic import. In a subsequent paper[3] the finer details of the microscopic characteristics of this same material will be presented.

From the Department of Pathology, University of California Medical School, San Francisco.

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HISTOLOGIC CLASSIFICATION

For the diagnosis of classical Hodgkin's disease the presence of Sternberg-Reed giant cells, fibrosis, abnormal lymph node pattern and eosinophils is required. From this prototype, two variants have been gradually defined, one possessing superficially many of the characteristics of a small cell lymphosarcoma, and the other possessing many character-

istics of a bizarre reticuloendothelial sarcoma. The classical type of Hodgkin's disease has been quite uniformly referred to as Hodgkin's granuloma, and the bizarre cellular and malignant-looking reticuloendothelial variant as Hodgkin's sarcoma (Hodgkin's lymphoreticuloma, Bersack[2]). That variant presenting the resemblance to lymphocytic lymphosarcoma has been called Hodgkin's lymphoma, Bersack[2]; atypical Hodgkin's, Warthin[23]; "early Hodgkin's disease"; or, more recently, paragranuloma, Jackson and Parker.[11]

Pre-Hodgkin's disease changes in lymph nodes have been described, consisting of reticuloendothelial hyperplasia and distortion of the lymph node pattern. However, these are by no means specific, and their significance is doubtful. In fact, a positive diagnosis of Hodgkin's disease cannot be made in the absence of Sternberg-Reed cells. In their absence, to be pleased with having correctly guessed the subsequent development of a Hodgkin's disease process is to ignore the many times that the diagnosis of Hodgkin's disease without Sternberg-Reed cells will have been an error. In the slides examined for this report, no characteristic "pre-Hodgkin's disease" changes could be identified in lymph nodes immediately adjacent to nodes frankly involved with Hodgkin's disease, nor in uninvolved portions of a partially diseased lymph node.

Although the microscopic separation of Hodgkin's disease into paragranuloma, granuloma and sarcoma varieties is justified and well established in the literature, it is not possible, after reviewing the material in this paper, to entirely support the statement by Jackson and Parker[11] that "It should become clear . . . that any description [of Hodgkin's disease] that includes all three [variants] as a single form of the disease must, of necessity, be inaccurate and of little practical value."

In the first place, statistically drawn conclusions regarding data from the two marginal variants (paragranuloma and sarcoma) of Hodgkin's disease must be made with great care. The very fact that they are variants of a classical type infers that they likewise merge imperceptibly with structurally similar tumors that are not Hodgkin's disease. It is this very merging of structural types that has led so many workers to feel that Hodgkin's disease is not an entity, but instead is a variety of lymphosarcoma, and of similar etiological background. It follows that in collecting examples of Hodgkin's paragranuloma and Hodgkin's sarcoma, certain errors are bound to creep in which will contaminate statistical analyses. It is quite possible that the only Hodgkin's lymphomas and Hodgkin's sarcomas that are completely beyond suspicion are those examples which have passed through or developed into a proven Hodgkin's granuloma stage.

This error in classification is most likely to be made in the case of Hodgkin's sarcoma, because of the tendency to place in that category many poorly defined pleomorphic and large-celled reticuloendothelial sarcomatous tumors. Such being the case, it is likely that any reported series of so-called Hodgkin's sarcoma will be somewhat contaminated with non-Hodgkin's disease cases, and thus tend more nearly to approach the usual sex ratios and age incidence of lymphosarcomas in general.

Hodgkin's paragranuloma variant may rather closely resemble a malignant lymphocytoma. In any series of Hodgkin's paragranuloma, it is likely that some will actually be malignant lymphocytoma, and not Hodgkin's paragranuloma. Some may maintain that the presence of Sternberg-Reed cells proves the diagnosis. That is almost correct. Unfortunately, however, these cells are only peculiar types of reticuloendothelial cells, which, although highly characteristic, do present variations, and are not absolutely pathognomonic. This thus permits certain individual interpretations as to their presence or absence.

Of the 11 cases in this series in which the patients showed the longest survival (5 to 14 years), in only one did biopsy reveal the characteristics of the paragranuloma variant—and in that case the patient survived only five years. In nine of these cases the specimen showed the classical Hodgkin's granuloma pattern, and in one (with the patient having a five and one-half year survival) the lesion commenced as a giant follicular lymphoma tumor. These data do not support the thesis of a relatively prolonged course of the disease with the Hodgkin's paragranuloma variant, although admittedly the number of patients studied is too small to be statistically conclusive.

An analysis of the seven cases diagnosed at the time of the original biopsy as Hodgkin's sarcoma reveals that the mean survival time was eight months from the onset of the disease. This more rapid course for Hodgkin's sarcoma has been frequently noted. The average age of patients in this group of cases is 27 years, and five of them were males.

AGE AND SEX INCIDENCE

Hodgkin's disease may occur at any age. The youngest patient of record was autopsied at four and one-half months of age, and was presumably born with the disease. The case was described by Priesel and Winkelbauer,[17] who state that one month before the infant's birth, a lymph node removed from the mother was diagnosed as a lesion of Hodgkin's disease. The mother died but autopsy was not done.

In this reported series, the greatest age at the time of onset was 73 years and the least was seven years. The age distribution data (Table 1) compares favorably with those reported in the literature (Wallhauser,[22] Baker[1]), and the tendency for the onset before the age of 40 was evident.

The ratio of males to females, 2.4:1, was similar to that found throughout the literature. Below the age of 15 there were 13 cases, all in boys. This very great predominance of males in this age group has been noted by Goldman[10] and Smith,[19] and to a lesser extent by Jackson and Parker.[11]

TABLE 1.—*Age of Patients at Onset of Hodgkin's Disease*

Age in Years	*Males**	*Females†*	*Total*
1-10	7	0	7
11-20	10	3	13
21-30	31	13	44
31-40	20	10	30
41-50	20	6	26
51-60	11	10	21
61-70	5	2	7
Over 70	2	0	2
Total	106	44	150

*Youngest, 7; oldest, 73.
†Youngest, 15; oldest, 65.

CLINICAL CHARACTERISTICS

The average patient noted on his first entry between two and three signs and symptoms; 4.5 per cent had only one, 25 per cent noted two, and 44 per cent indicated three complaints. As shown in Table 2, malaise was most frequently referred to (17 per cent). Cough was next (10 per cent), then night sweats, weight loss and dyspnea (7 per cent each) were noted. Following the incidence of fever (6 per cent), abdominal pain, back pain, neck, arm or shoulder pain and locally enlarged nodes were each noted by approximately 5 per cent of the patients. In six cases (2 per cent) the disease was diagnosed before any signs or symptoms were noted by the patient (see Table 2).

The location of the originally noted tumors (Table 3) was much as that reported by other observers (Baker,[1] Slaughter and Craver,[18] Smith[19]), with the most frequent sites of apparent origin being in the neck. There is nothing in these data which supports Symmer's[20] statement that the deep nodes are probably ten times more commonly affected than the superficial nodes. Although, as in other series, the left cervical nodes were clearly the site of most frequent origin, there was little else to support the occasionally suggested explanation that the greater incidence of left neck tumors is related to the emptying of the thoracic duct on that side, and hence may represent a spread of the disease from some internal site via that duct to the neck. One point against the theory that the frequency of cervical node involvement by Hodgkin's disease may be explained by a nasopharyngeal "portal of entry," is the rarity of tonsillar and pharyngeal Hodgkin's disease.

TUBERCULOUS, SEROLOGICAL AND OCCUPATIONAL HISTORIES

In 121 patients with Hodgkin's disease a family history of tuberculosis was obtained in 15 per cent. In California the figure for similar data in the normal population is 0.5 per cent (Telford and Gartin-White[21]). In spite of repeated attempts to connect Hodgkin's disease etiologically with some form of tuberculosis, all efforts have failed and there remain but two interesting correlations. One is the often chronic inflammatory granulomatous appearance of the lesions of Hodgkin's disease, and the second is the consistently high percentage of negative tuberculin reactions in patients having Hodgkin's disease. Parker and Jackson[15] reported the greater frequency of healed and active tuberculosis in autopsies on patients with Hodgkin's disease (33 per cent) than in those having other lymphoma (5.3 per cent), cancer (14.6 per cent), or in general autopsies (19.3 per cent). Others also have noted this phenomenon. Baker,[7] however, felt that this increased incidence was questionable and in any case was overemphasized.

In the series of Hodgkin's disease, here reported, the incidence of healed and active tuberculosis was 17 per cent. In an equivalent general autopsy group the percentage of tuberculous lesions (healed and active) was 11 per cent, in the cancer group 4 per cent and in the lymphoma (excluding Hodgkin's disease) group 13 per cent. The tuberculin test was done in 34 cases, with negative reaction in 31 and positive in three. Nobécourt[13] noted this and suggested that this tuberculin anergy might be the explanation of the increased incidence of tuberculosis in Hodgkin's disease. A low incidence of positive reactions to tuberculin tests also may occur with other diseases of the reticuloendothelial system (such as leukemias and lymphosarcoma) which may be caused by that system being "blocked out," with resultant anergy (Parker, Jackson, Fitzhugh and Spies[14]).

Various serological procedures on patients with Hodgkin's disease were performed. The Kolmer test was positive in 5 per cent of 100 cases. In all of 15 cases in which tests were carried out, Brucella and tularemia agglutinations were negative. Typhoid

TABLE 2.—*Initial Signs and Symptoms as Noted by 135 Patients**

Malaise	17%	No symptoms	2%
Cough	10%	Leg swelling	2%
Night Sweats	7%	Leg pain	1%
Weight loss	7%	Paralysis	1%
Dyspnea	7%	Choking	1%
Fever	6%	"Flu"	1%
Neck, arm and/or shoulder pain	5%	Diarrhea	1%
Back pain	5%	Jaundice	1%
Abdominal pain	5%	Pigmentation	1%
Enlarged nodes	4%	Hoarseness	1%
Pruritus	4%	Dyspepsia	1%
Chest pain	4%	Abdominal mass	0.3%
Anorexia	3%	Hemorrhagic tendencies	0.3%
Rash	3%	Ascites	0.3%

*Patients each noted an average of three symptoms.

TABLE 3.—*Site of Primary Tumor, Correlated with Survival Time (132 Cases)*

Location	*Percentage*	*Average Survival*
Neck	78%	42 months
Left	43%	
Right	32%	
Unspecified	21%	
Midline	1%	
Axilla	9%	30 months
Inguen	6%	43 months
Chest and abdomen	7%	30 months

and paratyphoid agglutinations in this group revealed increased titres for each of them in two instances. The cell-free filtrates of some Hodgkin's disease lymph nodes were serially passed in embryonated chicken eggs. Not only was an increased mortality demonstrated in these eggs (Bostick[4]), but increased cutaneous sensitivity reaction to their amniotic fluid is now apparent and is being studied further. This is all supportive evidence for the presence of a possible virus agent.

The histories of 126 patients were checked for exposure to animals, the object being to detect any correlations that might indicate the possibility of direct infection from animals. Special attention was directed toward contact with chickens. Seventy-five per cent were city dwellers and essentially free from animal contact. Seven per cent lived in rural communities and had had some slight contact with domestic animals. Eighteen per cent lived on farms with direct care of and exposure to animals. Two patients worked on a poultry farm. The proportion of farm dwellers among patients with Hodgkin's disease is no higher than it is in the general clinic population, and the number massively exposed to fowl is too small to warrant comment.

HODGKIN'S DISEASE AND GONADAL ACTIVITY

Gemmell[9] reported the case of a patient with Hodgkin's disease who developed it during her second pregnancy and had exacerbations during each subsequent pregnancy (two of them) and remissions between pregnancies (with the aid of treatment). He reviewed 57 cases of Hodgkin's disease in females, and concluded that in 46 per cent the onset of the disease was during a period of physiological amenorrhea (puberty, pregnancy, menopause, lactation). He proposed that cyclic ovarian activity is antagonistic to Hodgkin's disease and suggested that, where feasible, pregnancy should be terminated in women having Hodgkin's disease. Levrat and Jarricot[12] noted increase in symptoms during pregnancy in two women with Hodgkin's disease.

In the 35 females with Hodgkin's disease studied in the series here reported, 19 were having normal menstrual cycles at the first hospital entry after the onset of the disease. Eleven were menopausal and five were amenorrheic, making a total of 16 (46 per cent) in a non-cyclic ovarian phase. No cases of Hodgkin's disease occurred before the age of puberty (aet. 15) in females. Thirteen was the average age at the onset of menses for all females that developed Hodgkin's disease. These women had an average of 2.4 pregnancies each, and in four women the Hodgkin's disease was present during pregnancy. No particular untoward effect of the pregnancies on the course of the disease was remarked, and all were delivered of normal term infants. In view of the clearly greater incidence of Hodgkin's disease in males, and the apparent increased frequency of amenorrhea in females with Hodgkin's disease, there is some indication that ovarian hormones may play a part in the equilibrium of the disease. This might warrant further investigation.

BLOOD PICTURE

Much has been written on the blood picture in Hodgkin's disease. Most observers feel that there is a suggestive blood picture, but that it is not always present, and it is certainly not pathognomonic (Bunting,[5] Falconer,[8] Wiseman[24]). The more common finding is moderate, relative or absolute polynucleosis with lymphopenia. Mononucleosis tends to occur, and although the eosinophil count is usually normal, it may sometimes be very high. With progression of the disease a moderate progressive secondary type of anemia is the rule.

In the hemogram studies in this series of Hodgkin's disease no effort was made to evaluate the blood changes associated with the progression of the disease. It was felt that an analysis of the average blood picture in patients before any treatment, and at least six months before death, would be most informative, especially in regard to a typical Hodgkin's disease blood picture (Table 4). It can be seen that a slight leukocytosis (12,750) is present and the polymorphonuclear neutrophil average is 70 per cent, which is perhaps slightly above normal. The average for the lymphocytes (18 per cent) is below normal and monocytes (7 per cent) are at the upper margins of the normal limits. The mean eosinophilic count was 4 per cent. This included one patient with 68 per cent eosinophilia in a total of 37,000 white blood cells. Not counting this patient, the mean eosinophil count was 2.5 per cent, which is still slightly above a strictly normal mean. The usual moderate anemia, with 12.2 grams hemoglobin and 4,400,000 red blood cells as mean values, was present.

TABLE 4.—*Blood Counts Before Treatment and at Least Six Months Before Death*

	Total Cases	*Mean*
Hgb.	40	12g ± 2.0
Erythrocytes	40	4,400,000 ± 650,000
Leukocytes	41	12,750 ± 9,600
Polymorphonuclear	42	70 ± 17.3
Lymphocytes	42	18 ± 6.2
Monocytes	42	7 ± 3.7
Eosinophils	42	4 ± 1.8
Basophils	41	0.4 ± 1.5

FEVER

The occurrence of cycles of fever in cases of advanced Hodgkin's disease was noted by Pel[16] and Ebstein[6] and the occurrence of fever in Hodgkin's disease has been frequently remarked since. Baker[1] states that fever is uncommon when only peripheral nodes are involved, and is common when deeper nodes are invaded. Goldman[10] remarks that a rather characteristic feature is a pulse rate which is proportionally at a considerably higher level than the temperature.

In the fever data available in this reported series, it was felt that the information of greatest interest would be provided by trying to relate fever pattern

with survival, and also to correlate it with the site of apparent origin of the Hodgkin's disease. For these purposes, the fever was separated into five types: (1) Pel-Ebstein, (2) remittent, (3) intermittent, (4) continuous, (5) none. For each patient, the highest fever recorded was also noted. These data are arranged in Table 5.

TABLE 5.—*Survival Time After Onset, Correlated with Degree and Type of Fever**

Survival Time in Months	*Degree of Fever*	*Type of Fever*
3	39.4° C	2, 1, 2-4, 3-5
6	37.0	1
9	38.8	1, 1, 1, 1, 2-3, 3, 3-5, 4
15	39.0	1, 1, 2, 5
20	38.8	1, 1, 1, 1, 1, 3, 3-5, 5
30	38.8	1, 1, 1, 5
40	37.8	2-3, 3-5, 3-4, 5
50	39.4	1, 1, 1
60	38.6	1, 2-3, 3
80-140	37.5	2-3, 3-5, 5, 5, 5, 5

*Type 1, Pel-Ebstein; Type 2, Remittent; Type 3, Intermittent; Type 4, Continuous; Type 5, None.

TABLE 6.—*Site of Primary Tumor, Correlated with Degree and Type of Fever**

Site	*Mean Maximum Fever*	*Type of Fever** *Type*	*Percentage*
All areas of neck and axillas	38.4° C	1	41
		3	18
		5	19
All abdominal sites	39.0	1	50
		3	17
		5	0
All inguinal sites	38.1	1	33
		3	17
		5	33

*See Table 5.

When the cases of Hodgkin's disease are grouped according to the number of months the patients survived, and the type of fever of each group is examined, differences are noted. Of those surviving up to 20 months, only 7 per cent (two cases in 28) were afebrile, whereas 50 per cent had Pel-Ebstein fever, and about 45 per cent had the other varieties of fever. However, in those surviving five years or more, 50 per cent were afebrile, and only 10 per cent had Pel-Ebstein fever. Calculation of the averages of the highest temperatures of each of these survival groups revealed little of significance, although it showed a tendency for those patients with the longest survival to have the lower average maximum temperature.

Correlating the fever type and average maximum temperatures with the apparent primary site of origin of the disease (Table 6) revealed certain tendencies. The average maximum temperature in cases in which the primary site was abdominal was 39.0°C., whereas if origin was in the neck and axilla the average was 38.4° C., and if inguinal 38.1° C. Also in no case in which the abdomen was the primary site was the patient afebrile, and yet 19 per cent of the patients with the neck and axilla as the primary site, and 33 per cent of those in which origin was in the inguen, ran an afebrile course.

SURVIVAL

Data on survival are calculated from the onset of signs and/or symptoms. Since the precise times of onset are based mostly upon the patient's histories, they are not absolutely accurate. The overall average number of months of survival by this method is 41. In Table 7 the survivals have been broken down to show the age and sex of the patients in relation to survival time. The females not only have the disease less frequently, but tend on the whole to outlive the males. This difference is most pronounced in the decades over 40, whereas in the earlier decades the survival is about the same. Epstein[7] found a greater survival of females over males in 384 cases from the literature. However, Slaughter and Craver[18] did not find this difference in their 265 cases.

The survival in relation to the apparent sites of primary tumors is shown in Table 8. The survival for those with the disease starting in the neck or axilla is 41 months, and in the inguinal nodes 42 months, whereas the average survival for five patients with the disease starting in the abdomen or chest is 30 months (although one is yet alive 12 years after onset). These figures represent only a possible trend of survival, since too few cases are available for statistical study.

TREATMENT

X-ray alone was used in the treatment of the great majority of cases. Table 8 indicates that 39 patients out of the 55 for whom the time of death

TABLE 7.—*Survival Time After Onset*

Age in Years	*Male* *No. of Cases*	*Male* *Sur. in Months*	*Female* *No. of Cases*	*Female* *Sur. in Months*
0-10	3	30	0	....
11-20	3	34	0	....
21-30	14	32	2	31
31-40	6	36	3	21
41-50	9	35	2	72
51-60	7	50	4	86
61-70	1	65	0	....

Average survival: male, 37 months; female, 56 months; combined, 41 months.

TABLE 8.—*Survival Time Correlated with Therapy*

No. of Cases	*Therapy*	*Survival time in months*
2	None	5
39	X-ray	41
2	X-ray plus Coley's toxin	40
1	X-ray plus radioactive phosphorus	75
4	X-ray plus surgical excision	71
1	X-ray plus Coley's toxin plus cacodylate	102
1	X-ray plus splenectomy	69
1	Gland resection alone	23
1	"Hodgkin's vaccine" only	13
1	Fowler's solution only	23
1	"Hodgkin's vaccine" plus x-ray	23

is known received x-ray alone and had a mean survival time of 41 months. The total number treated by other methods was too small to use as a basis of conclusions as to comparative value of methods of treatment. The short survival of the two patients who received no treatment reflects not so much the lack of treatment as the fact that the disease had so far progressed at the time of entry that therapeutic efforts were considered unwarranted. Surgical excisions in selected cases presenting localized surgically accessible tumor masses has been reported to result in some prolonged survivals, especially when followed by x-ray therapy (Slaughter and Craver[18]). Four patients in our series were treated in this manner. One survived 48 months, another 95 months, while another was alive until lost track of 11 years after the operation, and the fourth, who had a Hodgkin's sarcoma, lived only 11 months. In one case in which treatment was surgical excision alone the patient survived only 23 months.

The introduction of nitrogen mustard therapy is too recent to permit evaluation of therapeutic effects. Although apparently useful in selected cases, especially those in which the lesions are x-ray resistant, it produces severe toxic reactions. Its influence on actual survival time is not known, since it has been available for use for only about the same number of years that the average patient with Hodgkin's disease lives.

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